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(54) Title: COMPOSITIONS AND METHODS FOR TREATMENT OF SEXUAL DYSFUNCTION

(57) Abstract: Compositions and methods are provided for treatment of sexual dysfunction in mammals, including male sexual dysfunction, such as erectile dysfunction, and female sexual dysfunction. In one embodiment, a peptide-based composition including the peptide sequence Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH is administered. Methods of administration include injection, oral, nasal and mucosal administration.

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COMPOSITIONS AND METHODS FOR TREATMENT OF SEXUAL DYSFUNCTION5 **CROSS-REFERENCE TO RELATED APPLICATIONS**

 This application claims the benefit of the filing of U.S. Provisional Patent Application Serial No. 60/142,346, entitled *Compositions And Methods For Treatment Of Sexual Dysfunction*, filed on June 29, 1999, and U.S. Provisional Patent Application Serial No. 60/194,987, entitled *Compositions And Nasal Delivery Methods For Treatment Of Sexual Dysfunction*, filed on April 5, 2000, and the
10 specification thereof of each is incorporated herein by reference.

GOVERNMENT RIGHTS

 The U.S. Government has a paid-up license in this invention and the right in limited circumstances to require the patent owner to license others on reasonable terms as provided for by
15 the terms of Grant No. R43 GM60144 awarded by the awarded by the National Institute of General Medical Sciences of the National Institutes of Health of the U.S. Department of Health and Human Services.

BACKGROUND OF THE INVENTION20 **Field of the Invention (Technical Field):**

 The present invention relates to peptide constructs for the treatment of sexual dysfunction in animals, including both male erectile dysfunction and female sexual dysfunction, including methods and formulations for the use and administration of the same.

25 **Background Art:**

 Note that the following discussion refers to a number of publications by author(s) and year of publication, and that due to recent publication dates certain publications are not to be considered as prior art vis-a-vis the present invention. Discussion of such publications herein is given for more complete background and is not to be construed as an admission that such publications are prior art
30 for patentability determination purposes.

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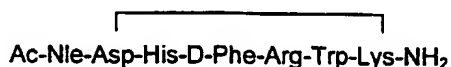
Sexual dysfunction, including both penile erectile dysfunction or impotence and female sexual dysfunction, are common medical problems. Significant effort has been devoted over the last twenty or more years to develop methods, devices and compounds for treatment of sexual dysfunction. While more effort has been undertaken for treatment of penile erectile dysfunction, female sexual
5 dysfunction is also an area to which significant research and effort has been devoted.

At present, one commonly used orally administered drug for treatment of sexual dysfunction in the male is Viagra®, a brand of sildenafil, which is a phosphodiesterase 5 inhibitor, increasing the persistence of cyclic guanosine monophosphate and thereby enhancing erectile response. There
10 are several other medical treatment alternatives currently available depending on the nature and cause of the impotence problem. Some men have abnormally low levels of the male hormone testosterone, and treatment with testosterone injections or pills may be beneficial. However, comparatively few impotent men have low testosterone levels. For many forms of erectile dysfunction, treatment may be undertaken with drugs injected directly into the penis, including drugs
15 such as papaverin, prostaglandin E₁, phenoxybenzamine or phentolamine. These all work primarily by dilating the arterial blood vessels and decreasing the venous drainage. Urethral inserts, such as with suppositories containing prostaglandin, may also be employed. In addition, a variety of mechanical aids are employed, including constriction devices and penile implants.

20 A variety of treatments have also been explored for female sexual dysfunction, including use of sildenafil, although the Food and Drug Administration has not specifically approved such use. Testosterone propionate has also been employed to increase or augment female libido.

Melanocortin receptor-specific compounds have been explored for use of treatment of sexual
25 dysfunction. In one report, a cyclic α -melanocyte-stimulating hormone (" α -MSH") analog, called Melanotan-II, was evaluated for erectogenic properties for treatment of men with psychogenic erectile dysfunction. Wessells H. et al., *J Urology* 160:389-393 (1998); see also U.S. Patent No. 5,576,290, issued November 19, 1996 to M.E. Hadley, entitled *Compositions and Methods for the Diagnosis and Treatment of Psychogenic Erectile Dysfunction* and U.S. Patent No. 6,051,555, issued
30 April 18, 2000, also to M.E. Hadley, entitled *Stimulating Sexual Response in Females*. The peptides used in U.S. Patent Nos. 5,576,290 and 6,051,555 are also described in U.S. Patent No. 5,674,839,

issued October 7, 1997, to V.J. Hruby, M.E. Hadley and F. Al-Obeidi, entitled *Cyclic Analogs of Alpha-MSH Fragments*, and in U.S. Patent No. 5,714,576, issued February 3, 1998, to V.J. Hruby, M.E. Hadley and F. Al-Obeidi, entitled *Linear Analogs of Alpha-MSH Fragments*. Melanotan-II is a peptide of the following formula:



Additional related peptides are disclosed in U.S. Patent Nos. 5,576,290, 5,674,839, 5,714,576 and 6,051,555. These peptides are described as being useful for both the diagnosis and treatment of psychogenic sexual dysfunction in males and females. These peptides are related to the structure of melanocortins.

In use of Melanotan-II, significant erectile responses were observed, with 8 of 10 treated men developing clinically apparent erections, and with a mean duration of tip rigidity greater than 80% for 38 minutes with Melanotan-II compared to 3.0 minutes with a placebo ($p = 0.0045$). The drug was administered by subcutaneous abdominal wall injection, at doses ranging from 0.025 to 0.157 mg/kg body weight. Transient side effects were observed, including nausea, stretching and yawning, and decreased appetite.

The minimum peptide fragment of native α -MSH needed for erectile response is the central tetrapeptide sequence, His⁶-Phe⁷-Arg⁸-Trp⁹ (SEQ ID 1). In general, all melanocortin peptides share the same active core sequence, His-Phe-Arg-Trp, including melanotropin neuropeptides and adrenocorticotropin. Five distinct melanocortin receptor subtypes have been identified, called MC1-R through MC5-R, and of these MC3-R and MC4-R are believed to be expressed in the human brain. MC3-R has the highest expression in the arcuate nucleus of the hypothalamus, while MC4-R is more widely expressed in the thalamus, hypothalamus and hippocampus. A central nervous system mechanism for melanocortins in the induction of penile erection has been suggested by experiments demonstrating penile erection resulting from central intracerebroventricular administration of melanocortins in rats. While the mechanism of His-Phe-Arg-Trp induction of erectile response has not been fully elucidated, it has been hypothesized that it involves the central nervous system, and probably binding to MC3-R and/or MC4-R.

Other peptides and constructs have been proposed which are ligands that alter or regulate the activity of one or more melanocortin receptors. For example, International Patent Application No. PCT/US99/09216, entitled *Isoquinoline Compound Melanocortin Receptor Ligands and Methods of Using Same*, discloses two compounds that induce penile erections in rats. However, these
5 compounds were administered by injection at doses of 1.8 mg/kg and 3.6 mg/kg, respectively, and at least one compound resulted in observable side effects, including yawning and stretching. Other melanocortin receptor-specific compounds with claimed application for treatment of sexual dysfunction are disclosed in International Patent Application No. PCT/US99/13252, entitled *Spiropiperidine Derivatives as Melanocortin Receptor Agonists*.

Both cyclic and linear α -MSH peptides have been studied; however, the peptides heretofore evaluated have had an NH_2 group at the carboxyl terminus. See, for example, Wessells H. et al., *J Urology*, cited above; Haskell-Luevano C. et al., *J Med Chem* 40:2133-39 (1997); Schiöth H.B. et al., *Brit J Pharmacol* 124:75-82 (1998); Schiöth H.B. et al., *Eur J Pharmacol* 349:359-66 (1998); Hadley
15 M.E. et al., *Pigment Cell Res* 9:213-34 (1996); Bednarek M.A. et al., *Peptides* 20:401-09 (1999); U.S. Patent Nos. 6,054,556, 6,051,555 and 5,576,290; and, International Patent Applications PCT/US99/04111 and PCT/US98/03298. While significant research has been conducted in an effort to determine the optimal structure of α -MSH peptides, including a variety of structure-function, agonist-antagonist, molecular modeling and pharmacophore studies, such studies have relied upon
20 peptides with an art conventional NH_2 group at the carboxyl terminus. Further, it has long been believed that biologically active neuropeptides, including α -MSH peptides, are amidated, with an NH_2 group at the carboxyl terminus, and that such amidation is required both for biological activity and stability. See, for example, Metabolism of Brain Peptides, Ed. G. O'Cuinn, CRC Press, New York, 1995, pp. 1-9 and 99-101.

SUMMARY OF THE INVENTION (DISCLOSURE OF THE INVENTION)

The invention relates to a peptide that is a free acid or pharmaceutically acceptable salt thereof that includes the sequence His-Phe-Arg-Trp, His-D-Phe-Arg-Trp, homologs of His-Phe-Arg-
30 Trp or homologs of His-D-Phe-Arg-Trp. The peptide is preferably a cyclic peptide, and preferable

has a terminal -OH at the carboxyl terminus. In a preferred embodiment, the peptide is Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH.

The invention also includes pharmaceutical compositions of matter, including a peptide of this invention and a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier may be a buffered aqueous carrier, and preferably a saline or citrate buffered carrier.

The peptide of this invention, and pharmaceutical compositions of this invention, may be used for stimulating sexual response in a mammal. The invention thus also includes a method for stimulating sexual response in a mammal, in which a pharmaceutically sufficient amount of a composition including His-Phe-Arg-Trp, His-D-Phe-Arg-Trp, homologs of His-Phe-Arg-Trp or homologs of His-D-Phe-Arg-Trp is administered. In a preferred embodiment, the composition includes a peptide or pharmaceutically acceptable salt thereof of the formula Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH. The mammal may be male or female. In this method, the composition can also include a pharmaceutically acceptable carrier. The peptide or pharmaceutical composition may be administered by any means known in the art, including administration by injection, administration through mucous membranes, buccal administration, oral administration, dermal administration, inhalation administration and nasal administration. In a preferred embodiment, administration is by nasal administration of a metered amount of a formulation including an aqueous buffer, which buffer may be a saline or citrate buffer.

A primary object of the present invention is a melanocortin receptor-specific pharmaceutical for use in treatment of sexual dysfunction.

A second object is to provide a peptide-based melanocortin receptor-specific pharmaceutical for use in treatment of male sexual dysfunction, including erectile dysfunction.

Yet another object is to provide a peptide-based melanocortin receptor-specific pharmaceutical for use in treatment of female sexual dysfunction.

Yet another object is to provide a peptide-based melanocortin receptor-specific pharmaceutical for use in treatment of sexual dysfunction which is effective by intravenous administration at doses of less than 25 µg/kg of body weight, and preferably at doses of less than 0.5 µg/kg of body weight.

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Yet another object is to provide a peptide-based melanocortin receptor-specific pharmaceutical for use in treatment of sexual dysfunction which is effective by nasal administration at doses of less than 75 µg/kg of body weight, and preferably at doses of less than 25 µg/kg of body weight.

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Yet another object is to provide a peptide-based melanocortin receptor-specific pharmaceutical for use in treatment of sexual dysfunction with substantially reduced incidence of undesirable side effects.

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A primary advantage of the present invention is that it is therapeutically effective at doses that do not cause deleterious side effects, such side effects including nausea, yawning, stretching, decreased appetite and other effects observed with Melanotan-II.

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A second advantage of the present invention is that it provides compositions with a larger therapeutic window between desired therapeutic effects and the onset of undesired side effects than other melanocortin receptor-specific agents for the intended purpose.

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Yet another advantage of the present invention is that it provides compositions with a greater safety margin between desired therapeutic effects and the onset of undesired side effects than other melanocortin receptor-specific agents for the intended purpose.

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Yet another advantage of the present invention is that it provides a peptide-based melanocortin receptor-specific pharmaceutical for use in treatment of sexual dysfunction which is efficacious at significantly lower doses than Melanotan-II or other melanocortin receptor-specific agents.

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Yet another advantage of the present invention is that it provides a peptide-based melanocortin receptor-specific pharmaceutical for use in treatment of sexual dysfunction which is pharmaceutically active more rapidly following administration than Melanotan-II or other peptide-based melanocortin receptor-specific agents.

5

Yet another advantage of the present invention is that it provides a peptide-based melanocortin receptor-specific pharmaceutical for use in treatment of sexual dysfunction which, because of increased efficacy at low doses, may be administered by delivery systems other than art conventional intravenous, subcutaneous or intramuscular injection, including but not limited to nasal delivery systems and mucous membrane delivery systems.

10

Other objects, advantages and novel features, and further scope of applicability of the present invention will be set forth in part in the detailed description to follow, taken in conjunction with the accompanying drawings, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention. The objects and advantages of the invention may be realized and attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

15

BRIEF DESCRIPTION OF THE DRAWINGS

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The accompanying drawings, which are incorporated into and form a part of the specification, illustrate several embodiments of the present invention and, together with the description, serve to explain the principles of the invention. The drawings are only for the purpose of illustrating a preferred embodiment of the invention and are not to be construed as limiting the invention. In the drawings:

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FIG. 1 is a plot of the pharmacokinetic profile in rats intravenously administered 100 µg/kg body weight of **Compound 1**;

FIG. 2 is a plot of the pharmacokinetic profile in monkeys intravenously administered 50 µg/kg body weight of **Compound 1**;

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FIG. 3 is a plot of the pharmacokinetic profile in a monkey intranasally administered 50 µg/kg body weight of **Compound 1**;

FIG. 4 is a plot of the intranasal efficacy in rats of different amounts of **Compound 1**; and

FIG. 5 is a plot of pharmacokinetic profile in Beagle dogs intranasally administered 30, 150 and 650 µg/kg body weight of **Compound 1**.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

(BEST MODES FOR CARRYING OUT THE INVENTION)

In the listing of compounds according to the present invention, the amino acid residues have their conventional meaning as given in Chapter 2400 of the Manual of Patent Examining Procedure, 7th Ed. Thus, "Nle" is norleucine; "Asp" is aspartic acid; "His" is histidine; "D-Phe" is D-phenylalanine; "Arg" is arginine; "Trp" is tryptophan; "Lys" is lysine; "Gly" is glycine; "Pro" is proline; "Tyr" is tyrosine, and "Ser" is serine. "Ac" refers to a peptide or amino acid sequence that is acetylated.

The invention provides deamidated α-MSH peptides, which are peptides that include the core α-MSH sequence His-Phe-Arg-Trp, His-D-Phe-Arg-Trp, or homologs or analogs of either of the foregoing, in which the peptide is deamidated, which is to say that it does not include an -NH₂ group at the carboxyl terminus. In a preferred embodiment, the deamidated α-MSH peptides of this invention have an -OH group at the carboxyl terminus, and are thus a free acid form of peptide.

In a preferred embodiment, the invention provides the peptide

Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH

Compound 1

The peptide of **Compound 1** has a formula of C₅₀H₆₈N₁₄O₁₀, and a net molecular weight of 1025.18. This peptide may be synthesized by solid-phase means and purified to greater than 96% purity by HPLC, yielding a white powder that is a clear, colorless solution in water.

In general, the peptide compounds of this invention may be synthesized by solid-phase synthesis and purified according to methods known in the art. Any of a number of well-known procedures utilizing a variety of resins and reagents may be used to prepare the compounds of this invention.

5

The peptides of this invention may be in the form of any pharmaceutically acceptable salt. Acid addition salts of the compounds of this invention are prepared in a suitable solvent from the peptide and an excess of an acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. The acetate salt form is especially useful.

10 Where the compounds of this invention include an acidic moiety, suitable pharmaceutically acceptable salts may include alkali metal salts, such as sodium or potassium salts, or alkaline earth metal salts, such as calcium or magnesium salts.

The invention provides a pharmaceutical composition that includes a peptide of this invention
15 and a pharmaceutically acceptable carrier. The carrier may be a liquid formulation, and is preferably a buffered, isotonic, aqueous solution. Pharmaceutically acceptable carriers also include excipients, such as diluents, carriers and the like, and additives, such as stabilizing agents, preservatives, solubilizing agents, buffers and the like, as hereafter described.

20 **Routes of Administration.** Because, in part, of the increased potency of **Compound 1** and the other peptides of this invention, these peptides may be administered by means other than by injection. If it is administered by injection, the injection may be intravenous, subcutaneous, intramuscular, intraperitoneal or other means known in the art. The peptides of this invention may be formulated by any means known in the art, including but not limited to formulation as tablets,
25 capsules, caplets, suspensions, powders, lyophilized preparations, suppositories, ocular drops, skin patches, oral soluble formulations, sprays, aerosols and the like, and may be mixed and formulated with buffers, binders, excipients, stabilizers, anti-oxidants and other agents known in the art. In general, any route of administration by which the peptides of invention are introduced across an epidermal layer of cells may be employed. Administration means may include administration through
30 mucous membranes, buccal administration, oral administration, dermal administration, inhalation administration, nasal administration and the like. The dosage for treatment of male erectile

dysfunction is administration, by any of the foregoing means or any other means known in the art, of an amount sufficient to bring about an erection of the penis in a male. The dosage for treatment of female sexual dysfunction is administration, by any of the foregoing means or any other means known in the art, of an amount sufficient to bring about the desired response.

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The peptides of this invention may be formulated or compounded into pharmaceutical compositions that include at least one peptide of this invention together with one or more pharmaceutically acceptable carriers, including excipients, such as diluents, carriers and the like, and additives, such as stabilizing agents, preservatives, solubilizing agents, buffers and the like, as may be desired. Formulation excipients may include polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate. For injection or other liquid administration formulations, water containing at least one or more buffering constituents is preferred, and stabilizing agents, preservatives and solubilizing agents may also be employed. For solid administration formulations, any of a variety of thickening, filler, bulking and carrier additives may be employed, such as starches, sugars, fatty acids and the like. For topical administration formulations, any of a variety of creams, ointments, gels, lotions and the like may be employed. For most pharmaceutical formulations, non-active ingredients will constitute the greater part, by weight or volume, of the preparation. For pharmaceutical formulations, it is also contemplated that any of a variety of measured-release, slow-release or time-release formulations and additives may be employed, so that the dosage may be formulated so as to effect delivery of a peptide of this invention over a period of time.

In general, the actual quantity of peptides of this invention administered to a patient will vary between fairly wide ranges depending upon the mode of administration, the formulation used, and the response desired.

Nasal or Intrapulmonary Administration. By "nasal administration" is meant any form of intranasal administration of any of the peptides of this invention. The peptides may be in an aqueous solution, such as a solution including saline, citrate or other common excipients or preservatives. The peptides may also be in a dry or powder formulation.

In an alternative embodiment, peptides of this invention may be administered directly into the lung. Intrapulmonary administration may be performed by means of a metered dose inhaler, a device allowing self-administration of a metered bolus of a peptide of this invention when actuated by a patient during inspiration.

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The peptides of this invention may be formulated with any of a variety of agents that increase effective nasal absorption of drugs, including peptide drugs. These agents should increase nasal absorption without unacceptable damage to the mucosal membrane. U.S. Patents No. 5,693,608, 5,977,070 and 5,908,825, among others, teach a number of pharmaceutical compositions that may be employed, including absorption enhancers, and the teachings of each of the foregoing, and all references and patents cited therein, are incorporated by reference.

10

If in an aqueous solution, the peptide may be appropriately buffered by means of saline, acetate, phosphate, citrate, acetate or other buffering agents, which may be at any physiologically acceptable pH, generally from about pH 4 to about pH 7. A combination of buffering agents may also be employed, such as phosphate buffered saline, a saline and acetate buffer, and the like. In the case of saline, a 0.9% saline solution may be employed. In the case of acetate, phosphate, citrate, acetate and the like, a 50 mM solution may be employed. In addition to buffering agents, a suitable preservative may be employed, to prevent or limit bacteria and other microbial growth. One such preservative that may be employed is 0.05% benzalkonium chloride.

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It is also possible and contemplated that the peptide may be in a dried and particulate form. In a preferred embodiment, the particles are between about 0.5 and 6.0 μm , such that the particles have sufficient mass to settle on the lung surface, and not be exhaled, but are small enough that they are not deposited on surfaces of the air passages prior to reaching the lung. Any of a variety of different techniques may be used to make dry powder microparticles, including but not limited to micro-milling, spray drying and a quick freeze aerosol followed by lyophilization. With micro-particles, the peptides may be deposited to the deep lung, thereby providing quick and efficient absorption into the bloodstream. Further, with such approach penetration enhancers are not required, as is sometimes the case in transdermal, nasal or oral mucosal delivery routes. Any of a variety of inhalers can be employed, including propellant-based aerosols, nebulizers, single dose dry

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powder inhalers and multidose dry powder inhalers. Common devices in current use include metered dose inhalers, which are used to deliver medications for the treatment of asthma, chronic obstructive pulmonary disease and the like. Preferred devices include dry powder inhalers, designed to form a cloud or aerosol of fine powder with a particle size that is always less than about 6.0 μm .

5 One type of dry powder inhaler in current use is Glaxo's Rotahaler™, which dispenses a unit dose of powder into a tube, and employs patient suction for inhalation of the powder. Other, more advanced and preferred dry powder inhalers have been or are in development, which include propellants and the like.

10 Microparticle size, including mean size distribution, may be controlled by means of the method of making. For micro-milling, the size of the milling head, speed of the rotor, time of processing and the like control the microparticle size. For spray drying, the nozzle size, flow rate, dryer heat and the like control the microparticle size. For making by means of quick freeze aerosol followed by lyophilization, the nozzle size, flow rate, concentration of aerosoled solution and the like
15 control the microparticle size. These parameters and others may be employed to control the microparticle size.

In one preferred embodiment, a dry powder inhaler is employed which includes a piezoelectric crystal that deaggregates a dry powder dose, creating a small powder "cloud." Once
20 the powder cloud is generated, an electrostatically charged plated above the powder cloud lifts the drug into the air stream. The user with one relatively easy breath can then inhale the powder. The device may be breath activated, utilizing a flow sensor that activates the electronic components upon the start of inhalation, and thereby eliminating the need for coordination of activation and breathing rhythms by the user.

25

Induction of Penile Response. Both **Compound 1** and Melanotan-II induce penile erections in experimental rat models when administered by intravenous routes and by other routes, including nasal administration. However, **Compound 1** is approximately 100-fold more potent than Melanotan-II for inducing penile erection in the rat model. In intravenous dosing studies, penile
30 erection was induced by **Compound 1** in a broad range of concentrations, from 0.5 $\mu\text{g/kg}$ of body weight to 25 $\mu\text{g/kg}$ of body weight. At intravenous doses of 2 $\mu\text{g/kg}$ of body weight, **Compound 1**

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resulted in penile erection in 100% of rats tested, with approximately 50% of the rats having multiple erections during a 30 minutes observation period. By comparison, the optimal efficacious dose intravenously of Melanotan-II in the same rat model was 100 µg/kg of body weight.

- 5 The therapeutic window (the range from the desired therapeutic effect to observed adverse effects) for **Compound 1** is on the order of >1,000-fold, compared to a 3- to 4-fold therapeutic window for Melanotan-II. That is, the optimal efficacious dose of Melanotan-II is approximately one-third to one-fourth the dose that causes observed adverse effects. For **Compound 1**, the optimal efficacious dose is less than one-one thousandth the dose that causes observed adverse effects.
- 10 The significantly greater therapeutic window for **Compound 1** demonstrates that it is better tolerated than Melanotan-II.

- The potency of **Compound 1** is significantly higher than that of Melanotan-II, meaning that significantly less **Compound 1** is required for a desired effect, as compared to Melanotan-II. For
- 15 example, 2 µg/kg of body weight of **Compound 1** resulted in penile response by intravenous injection in rats, while 100 µg/kg of body weight of Melanotan-II was required for an equivalent penile response. The significantly higher potency results in less product being required. It further permits utilization of alternative delivery routes, including dermal, nasal and similar delivery routes, wherein higher quantities of drug may be required in order to achieve the desired effect. For example,
- 20 intranasal routes of administration typically have a bioavailability substantially less than that achieved with intravenous dosing, and thus more drug must be administered by intranasal routes in order to achieve the equivalent pharmacological response.

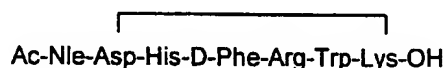
- Significant commercial advantage for **Compound 1** is demonstrated by the reduced effective
- 25 dose, compared to Melanotan-II, as a treatment or diagnostic for erectile dysfunction. Among the potential commercial advantages of **Compound 1** are improved effectiveness; lower costs of the product; improved convenience, particularly in that the lower dose permits non-conventional delivery methods that are not feasible with Melanotan-II doses; and improved safety with a decreased risk of side-effects.

Industrial Applicability:

The invention is further illustrated by the following non-limiting examples.

EXAMPLE 1 Peptide Synthesis

5 The peptide Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH was synthesized by standard solid phase peptide synthesis methods, and is a cyclic heptapeptide melanocortin peptide analog with a free acid at the carboxyl terminus and an acetylated amino group at the amino terminus, with the structure:



The peptide has a net molecular weight of 1025.18, and is supplied in an acetate salt form. The peptide is a white, odorless amorphous hygroscopic powder, soluble in 0.9% saline, composed of $\text{C}_{50}\text{H}_{68}\text{N}_{14}\text{O}_{10}$. For synthesis, an Fmoc-Lys(R^3)-p-alkoxybenzyl alcohol resin was transferred to a solid phase peptide synthesizer reactor with a mechanical stirrer. The R^3 group, such as 1-(1'-adamantyl)-1-methyl-ethoxycarbonyl (Adpoc), allyloxycarbonyl (Aloc) or 4-methyltrityl (Mtt), was removed and the next Fmoc-protected amino acid (Fmoc-Trp(Boc)-OH) was added to the resin through standard coupling procedures. The Fmoc protective group was removed and the remaining amino acids added individually in the correct sequence, by repeating coupling and deprotection procedures until the amino acid sequence was completed. After completion of coupling with the last Fmoc-amino acid derivative, Fmoc-Nle-OH, and cleavage of the Fmoc protective group, the exposed terminal amino group was acetylated with acetic anhydride and pyridine in N,N-dimethylformamide (DMF). The peptide-resin was dried and the Lys and Asp protective groups cleaved. The Lys and Asp deprotected peptide resin was suspended in a suitable solvent, such as DMF, dichloromethane (DCM) or 1-methyl-2-pyrrolidone (NMP), a suitable cyclic coupling reagent, such as 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TATU), 2-(2-oxo-1(2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU) or N,N'-dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCCI/HOBt) was added, and coupling initiated by use of a suitable base, such as N,N-diisopropylethylamine (DIPEA), sym-collidine or N-methylmorpholine (NMM). After cyclization, the peptide-resin was washed and the peptide cleaved from the resin and any remaining protective

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groups using trifluoroacetic acid (TFA) in the presence of water and 1,2-ethanedithiol (EDT). The final product was precipitated by adding cold ether and collected by filtration. Final purification was by reversed phase HPLC using a C₁₈ column. The purified peptide was converted to acetate salt by passage through an ion-exchange column.

EXAMPLE 2 Binding of Compound 1 and Melanotan-II to Melanocortin Receptors

The binding of **Compound 1**, made as in **Example 1** above, to selected melanocortin receptors was compared to binding of Melanotan-II. Melanotan-II was also made by conventional peptide synthesis, as generally described in **Example 1** above.

Relative binding was determined by competitive inhibition using α -MSH. B16-F1 melanoma cells were used as the source of MC1 receptors; HEK 293 cells, transfected with human melanocortin receptor sequences, were used as the source of MC3, MC4 and MC5 receptors; and Y1 cells were used as the source of MC2 receptors. A standard competitive binding assay protocol was following, using ¹²⁵I-NDP-MSH as the radioligand.

Utilizing the assay procedure, the following relative binding was determined:

TABLE 1					
RELATIVE BINDING (KI)					
COMPOUND	MC1-R (nM)	MC2-R	MC3-R (nM)	MC4-R (nM)	MC5-R (nM)
Compound 1	0.34	>10 ⁻⁶ M	0.25	11	120
Melanotan-II	0.12	>10 ⁻⁶ M	2.0	0.46	45

As shown above in **Table 1**, relative binding of **Compound 1** to MC4-R demonstrated, compared to Melanotan-II, on the order of 1/23 the affinity, while relative binding of **Compound 1** to MC3-R demonstrated, compared to Melanotan-II, on the order of eight-fold higher affinity. This substantial and unexpected difference in relative binding and affinity, particularly to MC4-R and MC3-R, is hypothesized to relate to the significantly increased potency of **Compound 1** as compared to Melanotan-II, the concomitant decrease in side effects with **Compound 1** as compared to

Melanotan-II, and the significantly greater therapeutic window with **Compound 1** as compared to Melanotan-II.

EXAMPLE 3 Agonist Activity of Compound 1

5 The agonist activity of **Compound 1**, made as in **Example 1** above, was evaluated by cyclic adenosine 3':5'-cyclic monophosphate (cAMP) detection using a commercially available cAMP kit (R&D Systems, DE0350, low pH). HEK 293 cells, stably transfected with human MC4-R, were used. **Compound 1** was evaluated by addition of each to cells both with and without concomitant addition of α -MSH, with α -MSH also used as a positive control. Following incubation, the medium was
10 aspirated and cell layers extracted. The total cAMP accumulation in fixed quantities of cell extract was determined by competitive immunoassay using the cAMP kit. These results are shown on **Table 2**.

TABLE 2				
cAMP Concentration (pMol/ml)				
Concentration of Test Compound	Compound 1	Compound 1 + 100 nM α-MSH	α-MSH	Blank (DMEM)
1×10^{-7} M	270.2	180.9	107.7	8.24
2.5×10^{-8} M	85.1	218.5	146.3	1.9
6.25×10^{-9} M	115.6	62.6	45.0	6.5
1.56×10^{-9} M	17.9	245.8	107.7	0.7
3.91×10^{-10} M	22.7	127.0	20.2	2.6
0.98×10^{-10} M	5.8	251.8	40.0	0.5

15 These results demonstrate that **Compound 1** exhibits agonist activity to MC4-R.

EXAMPLE 4 Induction of Penile Erections Using Compound 1 and Melanotan-II

The efficacious dose of **Compound 1**, made as in **Example 1** above, to induce penile erection in Sprague Dawley rats by intravenous dosing was determined. In the rat model of penile
20 erection, the optimal efficacious dose by intravenous administration is 100 μ g/kg body weight. Melanotan-II was also made by conventional peptide synthesis, as generally described in **Example 1** above. Male Sprague Dawley rats were administered **Compound 1**, in the indicated dose,

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Melanotan-II, or a saline negative control, and were observed for erections and side effects, including excessive grooming, yawning, vacuous chewing, hypoactivity, and heaving. It is known that Melanotan-II induces these side effects as doses as low as 300 µg/kg body weight. Table 3 sets forth the results obtained:

5

Table 3			
Induced Penile Erection in Sprague Dawley Rats by Intravenous Injection			
Drug Administered	Dose (µg/kg)	% Rats with Penile Erection	Number of Erections/ Rat/ 30 Minutes
Compound 1	0.5	50 %	0.5
Compound 1	0.75	50 %	0.5
Compound 1	1.0	100 %	1.0
Compound 1	2.0	100 %	2.0
Compound 1	5.0	100 %	1.8
Compound 1	10.0	100 %	2.5
Compound 1	25.0	50 %	0.5
Melanotan-II	10.0	17 %	0.3
Melanotan-II	100.0	75 %	1.0
Saline (Negative Control)	N/A	0 %	0

Two to four rats were observed in each group, with observation over a one-half hour period following administration. No adverse side effects were observed in any rat administered **Compound 1**. In this and comparable experiments, it was observed that **Compound 1** was efficacious at doses as low as 1 µg/kg of body weight when administered by intravenous injection, with efficacy determined by induction of penile erection in 100% of animals administered **Compound 1**. The comparable efficacious dose of Melanotan-II, with efficacy also determined by induction of penile erection in 100% of animals, was at least approximately 100 µg/kg body weight. This resulted in the unexpected conclusion that **Compound 1** was at least approximately 50-fold more potent for inducing erection in a rat model when administered by intravenous injection than is Melanotan-II. In other studies, no adverse side effects, including excessive grooming, yawning, vacuous chewing,

hypoactivity, or heaving, were observed on administration of intravenous doses of **Compound 1** as high as 3,000 µg/kg body weight.

5 **EXAMPLE 5 Pharmacokinetics in Rats Following IV Administration of Compound 1**

A sensitive bioassay, based on high affinity binding to MCRs, was used to monitor plasma levels of **Compound 1** in dosed rats. Rats were dosed intravenously with 100 µg/kg of **Compound 1**. A bi-phasic pharmacokinetic profile resulted, as shown in **FIG. 1**.

10

EXAMPLE 6 Pre-Formulation Studies for Nasal Delivery

A series of pre-formulation studies for nasal delivery were conducted. This study shows the stability of the peptide Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH, at a concentration of .825 mg/mL, over a period of twelve weeks, with storage at 40° C.

15

EXAMPLE 7 Formulations for Nasal Delivery

Based on the pre-formulation study of **Example 6**, two formulations were prepared. For the first, the peptide Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH was dissolved in a 0.9% saline solution, pH approximately 6.0, at a concentration of .825 mg per mL of solution (**Nasal Formulation 1**). In an alternative formulation, Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH was dissolved in a 50 mM citrate, pH approximately 6.0, also at a concentration of .825 mg per mL of solution (**Nasal Formulation 2**).

20

25 **EXAMPLE 8 Inhibition of Compound 1 Using Melanocortin Antagonist**

The effect of a nonselective melanocortin antagonist, SHU9119 (Hruby VJ, Lu D, Sharma SD, et al. *J Med Chem* 38:3454-3461 (1995)) to inhibit induction of penile erection with **Compound 1** was studied. A group of four Sprague Dawley rats were administered 5 µg/kg of SHU9119 by intravenous administration, and five minutes later 25 or 50 µg/kg of **Compound 1** in **Nasal Formulation 1** was administered by nasal administration. No erections were observed in the rats over the one-half hour observation period. No erections were observed in rats administered a saline control by nasal administration. In control groups, 100% of the rats administered the same dose of **Compound 1** by the same route of administration, but without pre-administration of SHU9119, had observed erections. **FIG. 4** shows the number of penile erections per rat during the initial 30 minute

30

period post-administration; as shown for the 25 µg/kg level, no penile erections were observed with pre-administration of SHU9119.

5 **EXAMPLE 9 Inhibition of Hypothalamus Accumulation Using Melanocortin Antagonist**

Tritiated **Compound 1** was prepared. In brief, a precursor to **Compound 1** was prepared using the general methods of **Example 1**, and the D-Phe amino acid was labeled with H³ using a tritiation reduction reaction. The resulting tritiated **Compound 1**, with a specific activity of 50 Ci/mM, was purified and tested. The nonselective antagonist SHU9119 was administered to Sprague
10 Dawley rats by intravenous administration. Five minutes following administration of SHU9119, 10 µCi of tritiated **Compound 1** was administered by nasal administration. In a control group of animals, the same dose of tritiated **Compound 1** was administered, without prior administration of SHU9119. Both groups were sacrificed five minutes following administration of tritiated
15 **Compound 1**, and the amount of tritium in the hypothalamus was detected. In animals pre-administered SHU9119, there was a decrease of 55% in the amount of detectable tritiated **Compound 1** within the hypothalamus, compared to animals not pre-administered SHU9119. The mean and standard deviation of counts per minute per 100 mg for animals pre-administered SHU9119 was 169.25 ± 23.13, and 75.75 ± 13.5 for animals not pre-administered SHU9119. Levels of tritiated **Compound 1** in the cerebral spinal fluid surrounding the hypothalamus were comparable .
20 in both groups of animals (161 ± 82 counts per minute per 100 mg for animals pre-administered SHU9119 compared to 165 ± 56 for animals not pre-administered SHU9119), indicating that the decrease in the hypothalamus following administration of SHU9119 is due to competition for specific receptors within the hypothalamus.

25 **EXAMPLE 10 Nasal Administration to Cynomolgus Monkeys**

Nasal Formulation 1 of **Example 6** was administered to cynomolgus monkeys by nasal spray, at a dose of approximately 50 µg per kg of body weight. Compared to intravenous injection of the same dose of Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH, the mean bioavailability of the peptide using **Nasal Formulation 1** was approximately 31.9% ± 2.7. In another series of
30 experiments, the mean bioavailability of the peptide using **Nasal Formulation 1** was 27.9% ± 9.7, and the mean bioavailability of the peptide using **Nasal Formulation 2** was 34.7% ± 15.6, in both cases again compared to bioavailability of the same quantity of peptide administered by intravenous

injection. In a related cardiovascular safety study using cynomolgus monkeys with intranasal administration of **Nasal Formulation 1**, an erection lasting approximately one hour was observed in one of four monkeys.

5 **EXAMPLE 11 Pharmacokinetic Profiles Following Administration to Cynomolgus Monkeys**

A sensitive bioassay, based on high affinity binding to MCRs, was used to monitor plasma levels of **Compound 1** in cynomolgus monkeys. Monkeys were dosed intravenously with 50 µg/kg of **Compound 1**. A bi-phasic pharmacokinetic profile resulted, as shown in **FIG. 2**. A selected monkey
10 was intranasally administered 50 µg/kg of **Compound 1** in **Nasal Formulation 1**, and the resulting pharmacokinetic profile is shown in **FIG. 3**.

EXAMPLE 12 Nasal Administration Dosing Study in Rats

In another series of experiments, a dosing study was conducted in rats by nasal
15 administration of from 15 µg per kg of body weight to 1500 µg per kg of body weight, using **Nasal Formulation 1**. Based on penile erectile response behavior, the peptide was efficacious at all dose amounts administered, and particularly from 25 µg/kg to 75 µg/kg, with pharmacologic effect observed over the range from 15 µg/kg to 1500 µg/kg. In addition, the response rate and side effects differed significantly from those demonstrated with nasal administration of Melanotan-II. With nasal
20 administration of the peptide of Melanotan-II, the penile erection response was primarily in the 2nd and 3rd ten-minute period, while with **Nasal Formulation 1** the penile erection response was primarily in the 1st and 2nd ten-minute period. Additionally, no adverse side effects were detected at any dosage level with **Nasal Formulation 1**, while adverse side effects were seen with administration of higher doses of the peptide of Melanotan-II. **Table 4** sets forth the comparative
25 data:

Table 4			
Induced Penile Erection in Sprague Dawley Rats by Intranasal Administration			
Drug Administered	Dose (µg/kg)	% Rats with Penile Erection	Number of Erections/Rat/30 Minutes
Compound 1	15	50 %	0.5
Compound 1	25	100 %	2.0
Compound 1	37	100 %	2.0
Compound 1	50	100 %	2.0
Compound 1	75	100 %	2.5
Compound 1	500	100 %	1.5
Compound 1	1000	100 %	1.5
Compound 1	1500	50 %	0.5
Melanotan-II	100	25 %	0.25
Melanotan-II	500	100 %	1.0
Saline (Negative Control)	N/A	0 %	0

EXAMPLE 13 Pharmacokinetic Profiles Following Administration to Beagle Dogs

A sensitive bioassay, based on high affinity binding to MCRs, was used to monitor plasma levels of **Compound 1** in Beagle dogs. The dogs were administered 0 (control), 30, 150 or 540 µg/kg of **Compound 1** in **Nasal Formulation 1** by nasal administration. The pharmacokinetic profile through four hours post-administration is shown in FIG. 5.

EXAMPLE 14 Administration For Treatment of Male Erectile Dysfunction

For treatment of male erectile dysfunction in human males with psychogenic erectile dysfunction, a total dose of 500 µg of **Compound 1** in **Nasal Formulation 1** is administered by means of a nasal administration metered dose device. The device dispenses a 100 µL spray volume, and is administered by the patient into a single nostril. If desired, erectile response is measured using an appropriate device, such as a Rigiscan (Dacomed).

EXAMPLE 15 Administration For Treatment of Female Sexual Dysfunction

For treatment of female sexual dysfunction in human females with psychogenic sexual dysfunction, a total dose of 500 µg of Compound 1 in Nasal Formulation 1 is administered by means of a nasal administration metered dose device. The device dispenses a 100 µL spray
5 volume, and is administered by the patient into a single nostril.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

10

Although the invention has been described in detail with particular reference to these preferred embodiments, other embodiments can achieve the same results. Variations and modifications of the present invention will be obvious to those skilled in the art and it is intended to cover in the appended claims all such modifications and equivalents. The entire disclosures of all
15 references, applications, patents, and publications cited above are hereby incorporated by reference.

CLAIMS

What is claimed is:

1. A peptide, comprising the sequence Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH.
5
2. The peptide of claim 1, consisting of the sequence Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH.
3. A composition of matter, comprising a peptide and a pharmaceutically acceptable
10 carrier, said peptide selected from the group consisting of Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH and pharmaceutically acceptable salts of Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH.
4. The composition of matter of claim 3, wherein the peptide consists of the sequence
15 Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH.
5. The composition of matter of claim 3, wherein the pharmaceutically acceptable carrier
is a buffered aqueous carrier.
6. A pharmaceutical composition for stimulating sexual response in a mammal,
20 comprising a peptide and a pharmaceutically acceptable carrier, said peptide selected from the group
consisting of Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH and pharmaceutically acceptable salts
of Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH.
7. The pharmaceutical composition of matter of claim 6, wherein the peptide consists of
25 the sequence Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH.
8. A pharmaceutical composition for stimulating sexual response in a mammal,
comprising a peptide and a pharmaceutically acceptable carrier, wherein said peptide is a free acid
or pharmaceutically acceptable salt thereof comprising a sequence selected from the group
30 consisting of His-Phe-Arg-Trp, His-D-Phe-Arg-Trp, homologs of His-Phe-Arg-Trp and homologs of
His-D-Phe-Arg-Trp.

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9. The pharmaceutical composition of claim 8, wherein said peptide is a cyclic peptide.

10. The pharmaceutical composition of claim 8, wherein said peptide has a terminal -OH at the carboxyl terminus.

5

11. The pharmaceutical composition of claim 8, wherein the peptide consists of the sequence Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH.

12. A method for stimulating sexual response in a mammal, comprising administering a pharmaceutically sufficient amount of a composition comprising a peptide or pharmaceutically acceptable salt thereof of the formula Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH.

10

13. The method of claim 12, wherein the mammal is a male.

15

14. The method of claim 12, wherein the mammal is a female.

15. The method of claim 12, wherein the peptide consists of the sequence Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH.

20

16. The method of claim 12, wherein the composition further comprises a pharmaceutically acceptable carrier.

25

17. The method of claim 12, wherein administering comprises administering by a method of administration selected from the group consisting of administration by injection, administration through mucous membranes, buccal administration, oral administration, dermal administration, inhalation administration and nasal administration.

18. The method of claim 17, wherein administering comprises nasal administration of a metered amount of a formulation comprising an aqueous buffer.

30

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19. The method of claim 18, wherein the aqueous buffer is a member selected from the group consisting of saline and citrate buffer.

20. A method for stimulating sexual response in a mammal, comprising administering a pharmaceutically sufficient amount of a composition comprising peptide wherein said peptide is a free acid or pharmaceutically acceptable salt thereof comprising a sequence selected from the group consisting of His-Phe-Arg-Trp, His-D-Phe-Arg-Trp, homologs of His-Phe-Arg-Trp and homologs of His-D-Phe-Arg-Trp.

21. The method of claim 20, wherein the mammal is a male.

22. The method of claim 20, wherein the mammal is a female.

23. The method of claim 20, wherein the peptide consists of the sequence Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH.

24. The method of claim of claim 20, wherein the composition further comprises a pharmaceutically acceptable carrier.

25. The method of claim 20, wherein administering comprises administering by a method of administration selected from the group consisting of administration by injection, administration through mucous membranes, buccal administration, oral administration, dermal administration, inhalation administration and nasal administration.

26. The method of claim 20, wherein administering comprises nasal administration of a metered amount of a formulation comprising an aqueous buffer.

27. The method of claim 26, wherein the aqueous buffer is a member selected from the group consisting of saline and citrate buffer.

SHEET 1/5

PROFILE IN RATS INTRAVENOUSLY ADMINISTERED

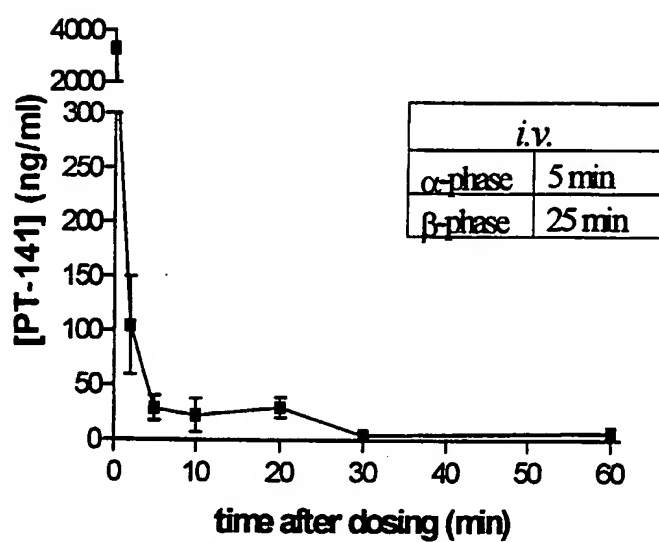


FIG. 1

SHEET 2/5

PROFILE IN MONKEYS INTRAVENOUSLY ADMINISTERED

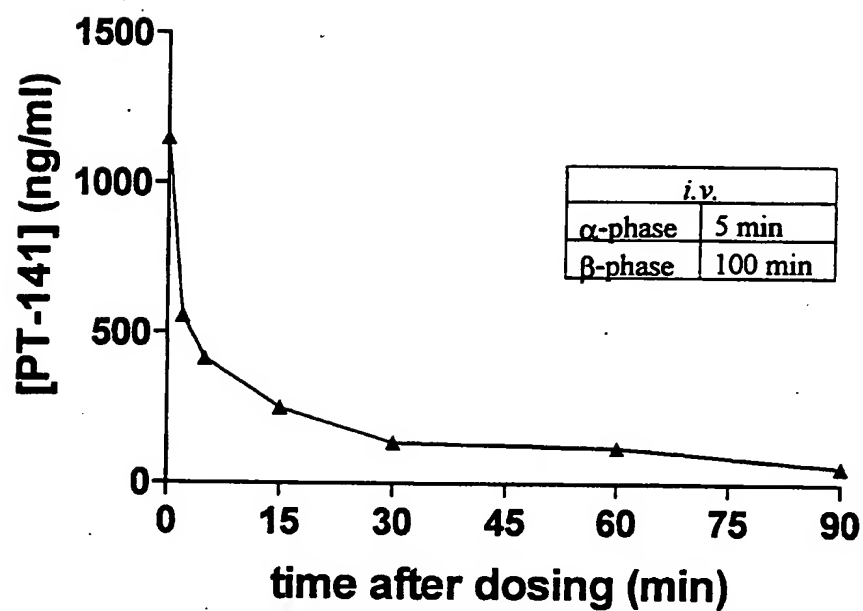


FIG. 2

SHEET 3/5

PROFILE IN MONKEYS INTRANASALLY DELIVERED

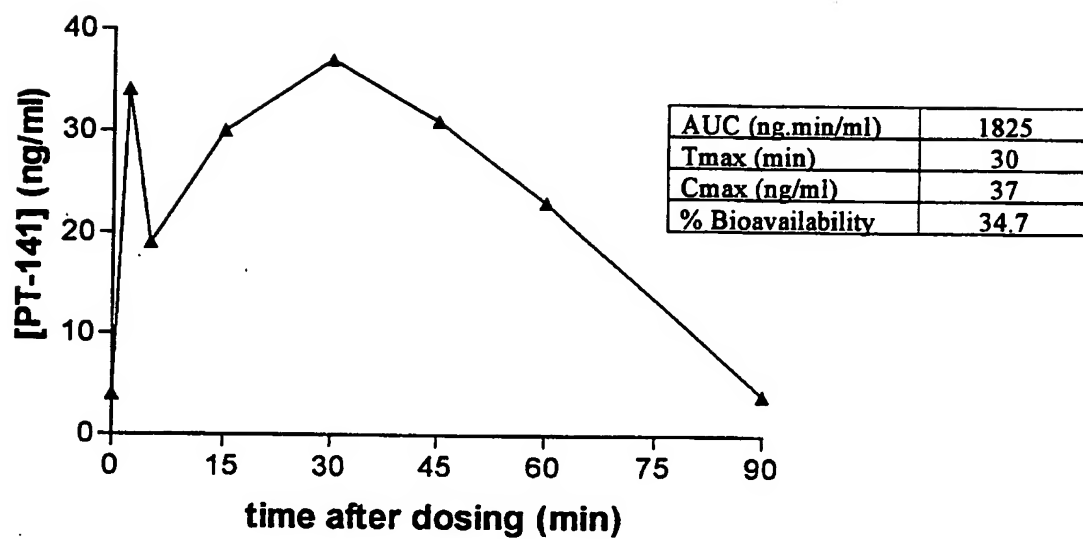
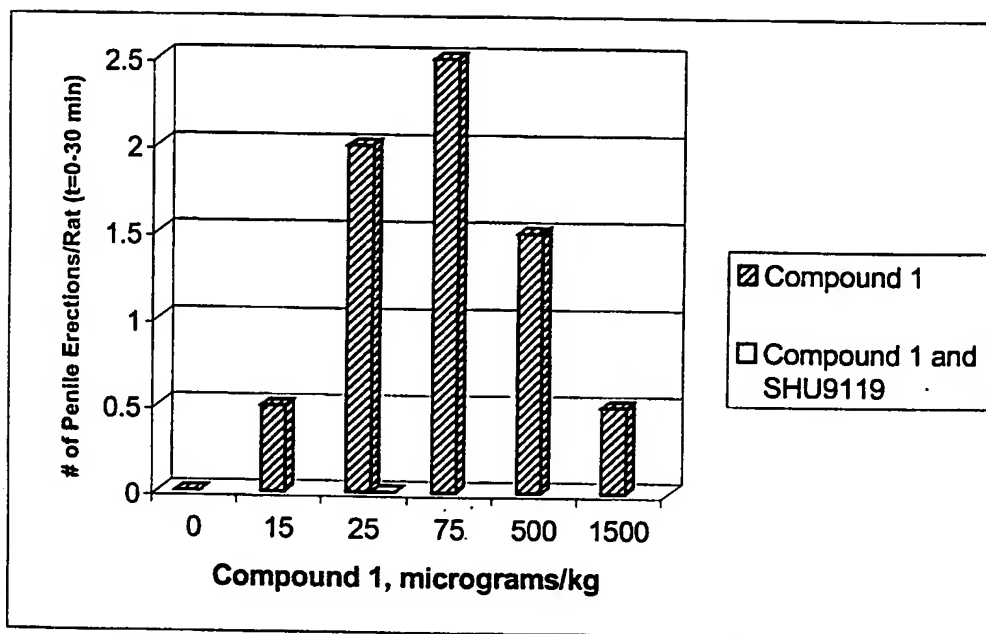


FIG. 3

SHEET 4/5



INTRANASAL EFFICACY OF COMPOUND 1 IN RATS

FIG. 4

SHEET 5/5

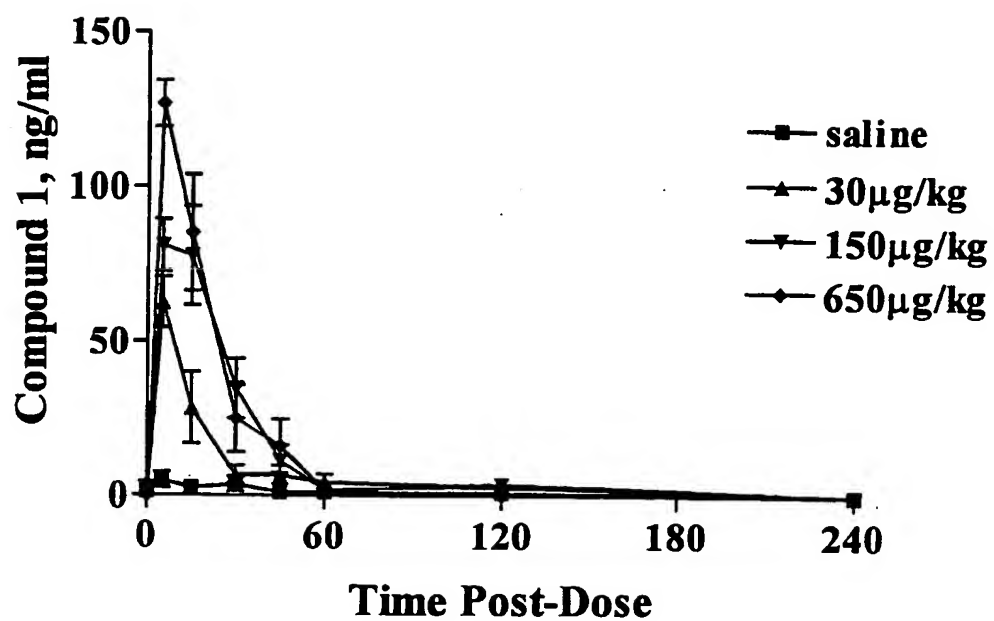
**Compound 1 Plasma Levels in
Beagle Dogs
(Intranasal)**

FIG. 5

SEQUENCE LISTING

<110> Palatin Technologies, Inc.

Blood, Christine

Shadiack, Annette

Bernstein, Joanna K.

Herbert, Guy W.

<120> Compositions and Methods for Treatment of Sexual
Dysfunction

<130> 70025-PCT-4

<140>

<141>

<150> 60/142,346

<151> 1999-06-29

<150> 60/194,987

<151> 2000-04-05

<150> PENDING

<151> 2000-06-28

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<170> PatentIn Ver. 2.1

<210> 1

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<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial

Sequence:alpha-melanocyte-stimulation hormone

tetrapeptide core sequence

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His Phe Arg Trp

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/18217

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 38/00, 38/08, 38/12.

US CL : 514/9, 11, 15, 16; 530/312, 317, 321, 328, 329; 424/9.1.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/9, 11, 15, 16; 530/312, 317, 321, 328, 329; 424/9.1.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched ...

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN-REGISTRY, CAPLUS, USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,576,290 A (HADLEY) 19 November 1996, see entire document.	1-27
Y,P	US 6,051,555 A (HADLEY) 18 April 2000, see entire document	1-27
Y,P	WO 99/64002 A1 (MERCK & CO., INC.) 16 December 1999, see entire document.	1-27

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

01 OCTOBER 2000

Date of mailing of the international search report

26 OCT 2000

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